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PERSPECTIVE

The Sicilian Gambit: Does It Help the Clinician?

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On May 8, 1997, a Clinical Tutorial was held during the Annual Scientific Sessions of the North American Society for Pacing and Electrophysiology [NASPE] to address the question: has the creation of the Sicilian Gambit (1) helped the clinician? The construct of the tutorial was a debate, and, as is often the case, there was truth on both sides. This review will summarize those truths and serve as a clinical guide with regard to the question addressed.

Background

With the development of an ever increasing array of antiarrhythmic drugs from the early 1970's to the present, clinicians became faced with the difficult task of choosing among them. Which, when, and how should an agent be chosen or avoided? What effects should be expected from the choice? In an attempt to facilitate a better understanding of antiarrhythmic drug (AAD) actions, and therefore appropriate usage, Vaughan-Williams (2–4), Singh (5–8), and others proposed a descriptive approach to the classification of AAD actions: class I, sodium channel blockade; class II, blockade of beta receptors; class III, prolongation of action potential duration (most often by blockade of outward potassium channel repolarizing currents); class IV, calcium channel blockade. Such actions could then be associated with probable clinical effects. For example, Na^+ blockade would translate into conduction impairment and prolonged refractoriness. Class III actions through delay of repolarization would prolong refractoriness. Since reentrant arrhythmias are critically dependent on an often sensitive balance between conduction and refractoriness, agents which alter either of these might be antiarrhythmic. Similarly, arrhythmias which depend upon automaticity might be suppressed through blockade of sympathetic stimulation via beta receptor blockade or by impairment of spontaneous depolarizing currents through Na^+ blockade. Soon thereafter it also became clear that such a classification system could also aid in an understanding of untoward AAD effects, as Na^+ channel blockade in patients with conduction disease or implanted devices could produce complete conduction impairment or elevated capture thresholds respectively. Drugs which alter refractoriness or conduction could also promote reentrant proarrhythmias. And, agents which prolonged action potential duration could promote torsades de pointes proarrhythmia through an association with early after depolarizations that may develop from inward current during the prolonged action potential plateau at its partially depolarized voltage. It also soon became apparent that some drugs had mixed actions, and subcategorization was required if clinical utility of the classification scheme was to be achieved. Hence, modification occurred such that the class I drugs were subdivided according to their effects on repolarization: class IA (typified by quinidine, procainamide, disopyramide) had both class I and III properties; class IB (typified by lidocaine, mexiletine, and tocainide) appeared to shorten repolarization slightly; and class IC (typified by flecainide and propafenone) exhibited potent Na^+ blockade with little or no effect on repolarization.

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Rationale for the Sicilian Gambit

With further usage, even this modification proved inadequate to fully describe the actions of many AAD. Additionally, it did not provide any direct link to the therapy of particular arrhythmias. For these and other reasons, a group of basic and clinical investigators held a series of meetings (the first in Sicily) and formulated a more comprehensive but complex approach that has come to be known as the Sicilian Gambit (SG) (1). The SG is not just a classification system of AAD actions, but rather, a system to promote a thoughtful approach to the application of an AAD to a specific arrhythmia. Students of the SG are encouraged to not merely choose a drug empirically, but rather, they are encouraged to apply knowledge about a particular arrhythmias' most likely mechanism(s), where known, and to identify a weak link or vulnerable parameter that may be affected by the application of an AAD which is known to possess feature(s) that may provide the desired corrective effect. In this construct, our arrhythmic drugs have to be considered not only by features they share in common but also by specific differences. Accordingly, a tabular descriptive format was developed which grouped AAD by their most dominant effects yet individually denoted many of their specific potential antiarrhythmic features—including channel(s) blocked, binding kinetics, receptors (e.g., beta, alpha, muscarinic, etc.) blocked, specific currents altered, the presence of extracardiac (e.g., central nervous system (CNS), autonomic nervous system (ANS), thyroid) antiarrhythmic actions, and common electrocardiographic (ECG) alterations.

Limitations

Although the SG improves upon the utility of the Vaughan Williams-Singh approach, and is a superb stimulus to young physicians and pharmacologists to develop structural and organized and interrelational thinking about AAD and their targets of therapy, it is so cmplex that practicing clinicians cannot easily commit the detailed table to memory. Hence it has been somewhat limited in its usefullness at the bedside despite its great utility in training and in stimulation of thought.

The SG is also limited, insofar as the clinician is concerned, in that even it does not provide details of all the antiarrhythmic-related actions and extra antiarrhythmic but clinically important features related to AAD administration that are necessary to know. For example, the SG does not consider the effects of metabolism and excretion. How should drug dosing be altered in disease states? Which agents have active metabolites and are they similar to or different than that of the parent compound? Consider the class I agent, procainamide, for example, which has a class III compound, NAPA, as its metabolite. Which agents have genetic pleomorphism in metabolism (such as propafenone) and how does this affect AAD usage? Such information is critical for optimal usage of the drug as the beta blocking properties of propafenone are only seen in the parent compound, which has high levels only in slow metabolizers or in high doses which overwhelm the capacity of the metabolizing enzyme. Also not discernible from the SG are which drugs are affected by interactions with other agents, or which themselves cause such interactions. For example, propafenone levels may be altered by coadministration with several beta blockers or quinidine; amiodarone may increase levels of most other AAD; amiodarone, quinidine, verapamil, and diltiazem, among others, may increase digoxin levels. The SG also does not consider the question: if an agent possesses more than one action, e.g., the beta blocker and K^+ blocking actions of d,L-sotalol, are they equally manifest across the dosing range? One cannot tell from the SG table that the beta blocker actions of d,L-sotalol tend to begin at 25 mg per day and plateau by 240–320 mg per day (assuming normal renal clearance) while the class III effects begin at 160 mg per day and continue up linearly through the suggested dosing range.

Drug-Disease Substrate Interactions

No action-based classification system can provide the clinician with highly drug specific information, about the important interactions which exist between AAD and the disease substrate. Lethal proarrhythmia, for example, is extremely rare with propafenone or flecainide in the structurally normal heart, despite their potent Na^+ channel blocking actions, but is quite worrisome in the diseased or ischemic ventricle where anatomic and/or functional effects on cell connections, gap junctions, membrane voltage, V_{max}, action potential duration, and more may all be altered and affect the manifestations of AAD administration. Drug application to the diseased heart may yield different actions than are seen in investigative studies employing normal Purkinje fibers or myocytes.

Similarly, no action-based classification system based on AAD effects can provide the clinician with the vital information required regarding inotropic, or organ toxic, or nuisance effects of an AAD when given to patients, or the effects of varying drug release formats which may affect drug selection. In the failing heart, for example, a negative inotropic drug would usually be considered unacceptable regardless of the channels or receptors it altered for its antiarrhythmic effects. Similarly, for benign arrhythmias, many physicians will avoid agents which can promote lupus (e.g., procainamide), thrombocytopenia (e.g., quinidine), or pulmonary fibrosis (e.g., amiodarone) which may be more serious disorders than the arrhythmia to be treated. For the noncompliant patient, a drug with a once daily format may be the only one to consider. To optimize even beta-blocker use, one must know about intrinsic sympathetic activity (as with pindolol, which is useful in the brady-tachy syndrome) and CNS penetration. The latter, when high (as with propranolol or metaprolol, but not with nadolol or betaxalol), may

increase CNS side effects (like nightmares and fatigue) but may decrease adverse central effects of other agents (such as mexiletine or tocainide tremor).

Summary

There is no perfect system at the level of the clinician. The SG attempts to bring some rationale to the application of an AAD to a specific arrhythmia—through knowledge of the arrhythmia's vulnerable parameter and the selection of an agent with features that may alter it. The SG is a vital step in the direction away from chaos or empiricism and toward rational drug usage aimed at improving efficacy and reducing untoward proarrhythmia or conduction effects. Nevertheless, even with the SG table in hand, the clinician must also apply a detailed knowledge of pharmacodynamics, pharmacokinetics, pharmacogenetics, tissue penetration, drug-disease interactions, drug-device interactions, and extra-cardiac actions and interactions to optimize the therapy of a patient given an antiarrhythmic pharmaceutical drug. This is a tall order, but unavoidable for proper AAD therapy.

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